BEVACIZUMAB IN OVARIAN AND CERVICAL CANCER – A RETROSPECTIVE CASE SERIES AT TAMPERE UNIVERSITY HOSPITAL

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KORHONEN KAMILLA: BEVACIZUMAB IN OVARIAN AND CERVICAL CANCER – A RETROSPECTIVE CASE SERIES AT TAMPERE UNIVERSITY HOSPITAL

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Tutkimme retrospektiivisesti bevasitsumabin, humanisoidun monoklonaalisen VEGF-vasta-aineen, kliinistä tehoa ja haittavaikutuksia sitä saaneilla potilailla.

Tutkimus sisälsi 38 munasarjasyöpää tai kohdunkaulansyöpää sairastavaa potilasta, jotka saivat bevasitsumabia joko yksin tai yhdessä tavanomaisen sytostaattihoidon kanssa. Bevasitsumabia (7,5mg/kg tai 15 mg/kg) annettiin suonensisäisesti kolmen viikon välein. Vastetta seurattiin seerumin CA 12-5 –mittauksin ja tietokonetomografiatutkimuksin. Päätetapahtumia olivat tauditon elinaika ja kliininen vaste.

Verenpaineen nousu oli hoidon tavallinen haittavaikutus, jota esiintyi 38 %:lla potilaista. Kahdelle potilaista kehittyi proteinuria, ja yhdellä potilaalla hoito aiheutti kuolemaan johtavan suoliperforaation.

Vasteosuus uusiutunutta munasarjasyöpää sairastavilla potilailla oli 30,8 % ja uusiutunutta kohdunkaulansyöpää sairastavilla 16,7 %. Taudittoman elinajan mediaani oli 17 kuukautta niillä munasarjasyöpäpotilailla, jotka saivat bevasitsumabia ensilinjan hoitona tai platinasensitiiviseen uusiutuneeseen tautiin.

Bevasitsumabihoito oli pääosin hyvin siedetty. Vakavimmista sivuvaikutuksista kärsivät raskaita hoitoja saaneet potilaat. Uusiutunutta munasarjasyöpää ja kohdunkaulansyöpää sairastavilla potilailla saatiin lupaavia tuloksia.

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SUMMARY

Purpose of Study

In this retrospective analysis we examine the clinical efficacy and safety of bevacizumab, an anti-VEGF antibody, in the treatment of ovarian (OC) and cervical cancer.

Materials and Methods

38 patients received bevacizumab either alone or in combination with standard chemotherapy.

Bevacizumab (7.5 mg/kg or 15 mg/kg) was administered intravenously every three weeks. CA 12-5 measurements and CT scans were performed to assess the response. Primary end points were progression-free survival (PFS) and clinical response.

Results

Hypertension was a common adverse event (38%). Two patients developed proteinuria and one patient experienced a fatal gastrointestinal perforation (GIP).

The response rate was 30.8% in patients with recurrent OC and 16.7% in patients with recurrent cervical cancer. The median PFS was 17 months in patients who received bevacizumab as a first-line treatment or patients with a platinum-sensitive recurrent OC.

Conclusion

Bevacizumab treatment was well tolerated. Results were encouraging especially in recurrent OC and cervical cancer.

1 INTRODUCTION

Ovarian cancer (OC) is associated with a high mortality rate, being the fourth most common cause of cancer-related deaths in women. An estimated 230,000 cases are diagnosed each year worldwide with 140,000 deaths annually (1). OC often develops insidiously and is diagnosed at advanced stage which attributes to the poor prognosis. OC is generally treated with a combination of paclitaxel and carboplatin to which the majority of the patients have a good response. However, most patients with an advanced stage ovarian cancer eventually relapse, often ultimately with platinum-resistant disease.

Recently, the expression of vascular endothelial growth factor (VEGF) in OC and cervical cancer has become an intense target of research. VEGF induces tumor angiogenesis fostering tumor growth and metastasis (2). Bevacizumab, a humanized monoclonal antibody against VEGF, inhibits VEGF-driven angiogenesis, thereby reducing tumor growth (3). In addition, VEGF increases the permeability of blood vessels which results in the formation of ascites, a characteristic of OC. Thus, the inhibition of VEGF decreases ascites formation (4) and improves the quality of life in patients with OC. It has also been suggested that VEGF blockade may improve the effect of chemotherapy. VEGF-induced increase in the permeability of blood vessels leads to a rise in the interstitial pressure impairing the access of most cytotoxic agents to the tumor tissue (5). As the effect of VEGF is restrained, the interstitial pressure declines, facilitating the diffusion of cytotoxic drugs.

Initial phase II trials gave promising results for treating relapsing OC with bevacizumab. Bevacizumab was given every three weeks either as monotherapy (6, 7) or in combination with metronomic cyclophosphamide (8, 9). Bevacizumab was generally well tolerated, although it increased the risk of intestinal perforation particularly in heavily pretreated patients (7). The efficacy of bevacizumab combined with platinum based combination therapy or weekly paclitaxel in OC has subsequently been shown in phase III trials both in primary and recurrent settings (10, 11, 12, 13). Bevacizumab was well tolerated and it increased progression free survival in all these trials.

Wright et al (14) studied the efficacy of bevacizumab in the treatment of recurrent cervical cancer in a small retrospective study. Bevacizumab was given in combination with 5-fluorouracil (5-FU). Combination therapy was well tolerated and effective in this group of heavily pretreated patients. Tewari et al (15) studied the use of bevacizumab in cervical cancer in a phase III study. The incorporation of bevacizumab with either platinum or nonplatinum chemotherapy significantly improved the median overall survival and progression-free survival in patients with recurrent, persistent, or metastatic cervical cancer.

Since 2006, bevacizumab has been in use for treatment of ovarian and cervical cancer at the Tampere University Hospital. The experience in the first-line setting has been published previously (16). In this study we describe our experience with bevacizumab primarily in patients with recurrent ovarian and cervical cancer.

2 MATERIALS AND METHODS

The study population consisted of 38 patients who received bevacizumab treatment for ovarian, tubal, primary peritoneal or cervical carcinoma at the Tampere University Hospital between January 1st 2006 and April 8th 2013. All patients who were prescribed bevacizumab between January 1st 2006 and September 31st 2011 were included.

The study was approved by the Institutional review board of Tampere University Hospital. The personal medical records of these patients were carefully examined and the following set of baseline information was collected: age, height and weight at the time of the first treatment, significant previous diseases, medications, tumor histology, grade and stage at the time of diagnosis and number of prior chemotherapeutic regimens.

The bevacizumab dose was recorded (either 7.5 mg/kg or 15mg/kg every three weeks) as well as concurrent chemotherapy and chemotherapy or other treatment following the bevacizumab treatment.

CA-125 measurements were performed before each treatment cycle and CT scans were taken according to the clinical practice, mostly at baseline and then approximately every three months. The size of the primary tumor was followed by routine ultrasound usually before every other infusion. The response rate and the duration of response for each patient were calculated. A response was defined as a decrease of CA-125 level according to the criteria of the Gynecologic Cancer Intergroup (17) or on the basis of radiologic indicators of response in a CT scan. If a patient had a complete response as shown on radiography, the response was determined complete. A mere decrease in CA-125 level was determined to be a partial response. A disease without progression or response was defined stable.

Progression free survival (PFS) was calculated from the date of the first bevacizumab dose to the date of progression, determined either by CA 125 measurement or CT scan, or death, whichever occurred first. Overall survival (OS) was defined as the period from the first bevacizumab treatment until death.
The data were analyzed using SPSS 20.0**.** The primary end point was PFS and the survival distribution was estimated using Kaplan-Meyer analysis.

To assess adverse events proteinuria was measured by dipstick before each infusion and routine blood pressure measurements were performed at home and at the hospital. Patients were monitored during bevacizumab infusions for any unexpected adverse events.

3 RESULTS

3.1 Characteristics of the patients

The study consisted of 38 patients of whom two patients had two separate regimens of bevacizumab treatment (as a first-line treatment and later for recurrent OC). The hospital records of all patients receiving bevacizumab from 2006 through 2013 were reviewed. Thirty patients had ovarian, tubal or primary peritoneal carcinoma (23 serous ovarian cystadenocarcinomas, two serous ovarian papillary cystadenocarcinomas, two serous tubal adenocarcinomas, two primary peritoneal carcinomas and one granulosa cell tumor). Seven patients had cervical carcinoma (of which four were adenocarcinomas, one was clear cell and two were squamous cell carcinomas) and one patient had an intraperitoneal leiomyosarcoma. Most patients had a poorly differentiated cancer that was widespread at the time of diagnosis. Five out of twenty patients with recurrent ovarian, tubal or primary peritoneal carcinoma had a platinum-resistant disease. The median age was 59.2 years. Twelve patients were given bevacizumab as a first line treatment and the rest of the patients consisted mostly of heavily pretreated patients, with a median of 2 previous therapy regimens (range [1, 7]). All but one of the patients had undergone an operation before the bevacizumab treatment and 13 patients had radiotherapy prior to receiving bevacizumab. The baseline characteristics of the patients are listed in Table 1.

Table 1. Baseline Characteristics.

Characteristic	First line treatment (N=12)	Platinum-sensitive recurrent OC, Bev+CCT (N=6)	Recurrent OC, Bev or Bev+C (N=13)	Recurrent cervical or other cancer* (N=8)
Age *(years)*				
Mean	63.1	54.3	60.5	49.9
Median	64	58.5	58	54
Range	[46, 79]	[25, 72]	[40, 82]	[28, 71]
Stage *(No.)*				
I	0	0	0	3
III	8	6	8	2
IV	4	0	3	2
Unknown	0	0	2	1
Grade *(No.)*				
1 (well differentiated)	1	2	1	2
2 (moderately differentiated)	2	0	5	4
3 (poorly differentiated)	8	4	6	2
Not graded	1		1	0
Prior chemotherapy regimens				
Median		1.5	4	2
Range		[1, 3]	[1, 7]	[1, 3]
Prior radiation *(No.)*				
No	12	4	9	1
Yes	0	2	4	7

Bev+CCT=Bevacizumab with combination chemotherapy
Bev= Bevacizumab as single agent
Bev+C= Bevacizumab with cyclophosphamide 50mg *p.o.* daily
*one leiomyosarcoma

3.2 Treatment

A total of 437 doses of bevacizumab were administered with a median of 12 doses (range [0, 25]) per patient. One patient had a dose interruption during her first infusion due to an unexpected adverse effect (allergic reaction). Infusions were given at a dose of 7.5mg/kg (29 patients) or 15mg/kg (9 patients) every three weeks. In one case the dose was increased from 7.5mg/kg to 15mg/kg due to disease progression, and for one patient the dose was lowered from 15 to 7.5mg/kg due to side effects (both severe proteinuria and hypertension). Infusions were continued until occurrence of marked side effects, disease progression or death. Seven patients were still receiving bevacizumab treatment at study termination.

Five patients received bevacizumab in combination with metronomic (50 mg/day) cyclophosphamide, 6 patients combined with capecitabine and 13 with current standard chemotherapy; either paclitaxel, docetaxel or gemcitabine combined with carboplatin or cisplatin. Eight patients received bevacizumab alone as monotherapy.

The concurrent treatments, along with the baseline characteristics and best clinical response in patients with ovarian and cervical cancer who received bevacizumab as monotherapy or combined with metronomic cyclophosphamide are presented in Table 2.

Table 2. Characteristics of the patients with recurrent OC or cervical carcinoma who received bevacizumab as monotherapy or combined with metronomic cyclophosphamide or capecitabine.

Patient	Age	Disease	Gradus	Primary stage	Treatment	Number of courses	Best response
1	68	Ovarian Granulosa Cell Tumor, liver metastasis			Bev	0	progression
2	55	Serous ovarian carcinoma	3	III	Bev	1	progression
3	58	Serous ovarian carcinoma	1	IV	Bev	19	PR
4	63	Serous ovarian carcinoma	2	IV	Bev	12	SD
5	54	Serous ovarian carcinoma	3	IIIC	Bev	12	SD
6	65	Serous ovarian carcinoma	3	IIIC	Bev	2	progression
7	74	Serous ovarian carcinoma	2	IIIC	Bev+C	7	PR
8	82	Primary peritoneal carcinosis	2	III	Bev+C	2	progression
9	40	Serous ovarian carcinoma	3	III	Bev+C	16	PR
10	53	Serous ovarian carcinoma	3	IIIC	Bev+C	8	PR
11	52	Serous ovarian carcinoma	2	IIIC	Bev+C	17	SD
12	65	Serous tubal adenocarcinoma	2	IV	Bev+C	6	progression
13	57	Serous tubal adenocarcinoma	3	IIIC	Bev+C	4	progression
14	39	Cervical squamous cell carcinoma	3	IB	Bev+Ca	2	progression
15	33	Cervical undifferentiated carcinoma	3	IVA	Bev+Ca	2	progression
16	71	Endocervcal adenocarcinoma	1	IV	Bev+Ca	21	PR
17	28	Cervical squamous cell carcinoma	3	IB	Bev+Ca	4	progression
18	48	Endocervical clear cell carcinoma	1	IIIB	Bev+Ca	22	SD
19	60	Cervical carcinoma NOS	unknown	IIIB	Bev+Ca	3	progression
20	60	Intraperitoneal leiomyosarcoma	unknown	unknown	Bev	22	SD

Bev = Bevacizumab as monotherapy
C = cyclophosphamide 50mg *p.o.* daily
Ca = capecitabine 1250 mg/m^2

3.3 Adverse events and efficacy

One case of intestinal perforation leading to death was observed in our study. Sixteen patients developed slight proteinuria, with severe proteinuria resulting in dose omission in one case and cessation of bevacizumab treatment in one patient. Eleven patients experienced hypertension that required medication and one case of grade 4 hypertension was observed. Clinically relevant bleeding or wound-healing complications were observed in 7 cases (5 nose bleeds, 1 case of hemoptysis, and one case of delayed postoperative wound healing). A summary of adverse events as compared to previous studies in patients with recurrent OC is presented in Table 3.

Table 3. Adverse Events. Patients with Recurrent OC.

Event	Present study: Recurrent OC, Bev or Bev+C (N=13)		Burger et al. (6)		Cannistra et al. (7)		Garcia et al. (9)	
	Any	G3-5	Any	G3-5	Any	G3-5	Any	G3-5
	No. (%)		%		%		%	
Hypertension	7 (54)	1 (7.7)	22.6	9.7	31.8	9.1	38.6	16
Proteinuria	3 (23)	0	32.3	1.6	15.9	0	44	4.3
GIP	1 (7.7)	1 (7.7)	0	0	11		6	2.8
Thrombosis/ embolism	0	0	3.2	3.2	9.1	9.1		4.3
Wound-healing complications	0	0	0	0	2.3	2.3		1.4
Nausea	1 (7.7)	0	20.9	4.8	34	2.3		2.8

Bev= Bevacizumab as single agent
Bev+C= Bevacizumab with cyclophosphamide 50mg *p.o.* daily
GIP= Gastrointestinal perforation

An adverse event led to dose omission in 5 other cases. Two patients developed grade 2 proteinuria, one patient had grade 4 hypertension as mentioned earlier, and wound dehiscence resulted in an interruption in bevacizumab treatment postoperatively.

In 5 cases the treatment was discontinued due to a side effect attributed to bevacizumab. These included severe proteinuria and hypertension, heavy nausea, hemoptysis, urticaria. One patient had an unexpected allergic reaction to bevacizumab, in which case the infusion had to be discontinued immediately. Treatment cessation due to progression-related or other side effects (including cancer-related pain, hydronephrosis and prolonged infection) occurred in 3 cases. Treatment was discontinued due to (cancer-related) death in one case and due to progression in 22 cases. In two cases the predesigned duration of treatment with bevacizumab was reached.

The overall response rate was 42.1% with 16 tumor responses of which nine were partial and seven complete. The response rate was 30.8% in patients with recurrent OC who received bevacizumab as monotherapy or combined with cyclophosphamide. Three responses were observed among patients with a

platinum-sensitive disease who received bevacizumab with standard combination chemotherapy. 11 responses occurred in patients in first-line treatment. These responses can be assumed as chemotherapy-related. One response (16.7%) was reported in patients with recurrent cervical cancer who received bevacizumab with capecitabine. Nine patients had stable disease.

According to the Kaplan-Meier analysis, the median progression-free survival (PFS) was 17 and 9 months in the subgroups of patients who were given bevacizumab as a part of first-line treatment or second-line treatment for platinum-sensitive relapse and patients with recurrent OC who received bevacizumab as monotherapy or combined with cyclophosphamide, respectively. Median overall survival (OS) was 18 and 24 months in the subgroups, respectively.

A positive correlation between mild hypertension and PFS was observed in patients with recurrent OC receiving bevacizumab as monotherapy or combined with cyclophosphamide. Median PFS in patients who did not suffer from bevacizumab-related arterial hypertension was 4.0 months (95% CI: 0.080 to 7.920) whereas it was 9.0 months (95% CI: 4.999 to 13.001) in patients with grade 1-2 hypertension and 2.0 months in the patient experiencing grade 4 hypertension (p=0.015 by Log Rank test).

4 DISCUSSION

4.1 Efficacy

The effect of bevacizumab as monotherapy or with metronomic cyclophosphamide has been shown previously in phase II trials. In the study conducted by Burger et al. (6) the response rate was 21.0%. Cannistra et al. (7) reported a response rate of 15.9% in a population of platinum-resistant patients. When bevacizumab was given in combination with cyclophosphamide in a study by Garcia et al. (9), the response rate was 24.0%. In our study, 30.8% of the patients with recurrent OC who were given bevacizumab as a single agent or combined with cyclophosphamide had a response. However, the percentage of patients with a platinum-resistant disease was somewhat lower compared to the above-mentioned studies by Burger et al. (6) and Garcia et al. (9). Taken into account the differences between the study populations the results in our study are still encouraging. The median duration of response and PFS are also in line with the previous studies. (Table 4)

Table 4. Objective Response in patients with recurrent OC in comparison to previous studies.

Response	Present study: Recurrent OC, Bev or Bev+C (N=13)	Burger et al. (6) (Bev) (N=62)	Cannistra et al. (7) (Bev) (N=44)	Garcia et al. (9) (Bev+C) (N=70)
Characteristics of the population -platinum-sensitive (%) -platinum-resistant (%)	 69.3 30.7	 58 42	 0 100	 60 40
Response rate - overall (%) -platinum-sensitive (%) -platinum-resistant (%)	 30.8 33 25	21.0	15.9	 24.0 33 12
Complete response (No.)	0	2	0	0
Partial response (No.)	4	11	7	17
Stable disease (No.)	3	32	27	44
Median duration of response *(months [range])*	8 [4, 12]	10.3	4.2 [1.7, 9.2]	N.D.**
Median PFS (months [95% CI])	9 [5.8 to 12.2]	4.7	4.4 [3.1 to 5.5]	7.2* [5.3 to 8.7]
Median OS (months [95% CI])	24 [4.0 to 44]	16.9	10.7	16.9 [11.4 to 25.2]

Bev= Bevacizumab as single agent

Bev+C = Bevacizumab with cyclophosphamide 50mg *p.o.* daily

*Time to progression

** N.D. = No Data

PFS and OS in patients receiving bevacizumab in the first-line setting combined with chemotherapy and then as maintenance were 17 months (95% CI: 9.609 to 24.391) and 17 months (95% CI: 14.383 to 19.617), respectively. In the GOG218 -study (10) the median PFS in the respective arm was 14.1 months. Perren et al. (11) reported a median PFS and OS of 19.8 and 36.6 months, respectively. In this ICON7-study (11) 70% of the patients had a stage IIIC or IV disease, compared to 92% in our population. The percentage of patients with a suboptimal debulking status was similar but the high number of patients with a widespread disease may explain the difference in the PFS and OS between these studies. Compared to the GOG218-study (10), the PFS in our study was higher but the OS lower. In their study, 26% of the patients had a stage IV disease at the time of diagnosis, compared to 33% in our study. The percentage of patients with a suboptimal debulking status was higher in the GOG218 population.

Patients with a platinum-sensitive recurrent OC who were given bevacizumab in combination with chemotherapy and then as maintenance, had a median PFS of 9 months and a median OS of 19 months. In the study conducted by Aghajanian et al. (12) the median PFS and OS were 12.4 and 33.3 months,

respectively. The OS in this study was longer than expected and assumed to be due to a high degree of censoring.

The activity of bevacizumab combined with 5-fluorouracil (5-FU) or its prodrug capecitabine has been shown in patients with metastatic colorectal cancer (19). In 2006 Wright et al (14) conducted a small retrospective analysis regarding the treatment of patients with cervical cancer with the above-mentioned combination therapy. The results were encouraging: Four out of six (67%) of the patients received clinical benefit from the treatment, which was overall well tolerated.

In our study, one of six patients with cervical cancer who received bevacizumab in combination with capecitabine had a response, which was partial and lasted for 16 months. In this group of patients we reported a median PFS of 2 months and median OS of 36.5 months. Wright et al. (14) reported a time to progression (TTP) of 4.3 months and a median OS of 5.1 months. Two responses were reported of which one was partial and one was complete.

4.2 Adverse events

Hypertension occurred more often (54%) in patients with recurrent OC than what previous studies have indicated (22.6%–38.6%) (6, 7, 9). However, hypertension was mainly of grade 1-2 (46%), with only one case of grade 4 hypertension which led to cessation of bevacizumab treatment. The incidence of grade 1-2 hypertension has been 12.9%–23% in previous studies, whereas grade 3-4 hypertension has occurred in 9.1–15.7% of the patients. Thus, mild hypertension was more common in our study than what has been reported previously, but severe grade 3-4 hypertension was more rare.

The incidence of hypertension among patients receiving bevacizumab as a first-line treatment or patients with platinum-sensitive recurrent OC was also higher in our study than in the studies regarding the use of bevacizumab as a part of first-line treatment and post-chemotherapy maintenance treatment. In this group five patients (28%) experienced grade 1-2 hypertension and one case of grade 3 hypertension was observed. Perren et al (11) have reported an incidence of 20 % in grade 1-2 hypertension. Grade 3 hypertension occurred with similar incidences in our population compared to Perren's (5.5% and 6%, respectively).

It has been observed previously that early severe hypertension is associated with a longer PFS. Emile et al. (20) found a difference of borderline significance in the progression-free survival between patients who experienced grade 3-4 hypertension during the first month of bevacizumab treatment compared to patients who did not. The positive correlation between early hypertension and anti-tumor activity has been

shown also in other tumor types (21, 22). Unless hypertension is life-threatening of untreatable, the cessation of bevacizumab treatment is therefore not generally indicated among these patients.

The association between hypertension and PFS was investigated in patients with recurrent ovarian or cervical cancer who received bevacizumab as monotherapy or in combination with metronomic cyclophosphamide (OC) or capecitabine (cervical cancer). A significant (p=0.015) difference in progression-free survival was observed between recurrent OC patients who experienced no hypertension, grade 1-2 hypertension or grade 3-4 hypertension during treatment cycle. The analysis consisted of 12 patients but is noteworthy that a statistically significant difference was observed even in such a small population. When we compared two groups with either no hypertension or any hypertension, the statistical significance subsided (p=0.092). Only one patient suffered from more severe (grade 3-4) hypertension and had an unfortunately short PFS which affected the analysis. There was no statistically significant difference between the groups in patients with cervical cancer.

One patient with recurrent OC experienced grade 2 proteinuria that led to treatment cessation. This patient had also hypertension. She had received six prior chemotherapy regimens, which may have increased the risk of adverse effects. One out of 12 patients (8.3%) receiving bevacizumab as a first-line treatment had grade 2 proteinuria leading to a dose omission. In previous studies, the incidence of grade 2 proteinuria has been at most 4%. Patients with cervical or other cancer had merely slight proteinuria (6 out of 8 patients, 75%). No events of grade 3 proteinuria were observed in our study.

One patient (7.7%) with recurrent OC, who had undergone two prior treatment regimens but no radiation, experienced a gastrointestinal perforation (GIP) which unfortunately led to death. Similar incidences of GIP have been described in previous studies (6, 7, 9). Recent or current bowel obstruction, advanced disease and chemotherapy-resistant disease have been suggested as risk factors for gastrointestinal perforation (7).

Overall, mild hypertension seemed to be more common in our study population than in other studies. Slight proteinuria was also common, but there were only two events of grade 2 proteinuria and no events of proteinuria of grade 3 or more. The incidence of GIP was not higher than in other studies and there were no cases of venous of arterial thromboembolism in our study. The incidence of thromboembolic events has been 3.2–9.1% in patients with recurrent OC and 6–11% in the studies regarding bevacizumab as a first-line treatment. Serious adverse events leading to treatment discontinuation occurred mainly in patients with recurrent disease with several prior chemotherapy regimens. Adverse events among patients receiving bevacizumab as a first-line treatment were mainly of grade 1 with only two treatment interruptions and one case of treatment cessation due to toxicity.

It is noteworthy that even patients with a very poor prognosis had benefit from bevacizumab treatment. Patients allergic to chemotherapeutic agents have been able to receive treatment and we recorded one response lasting 9 months in a patient with a platinum-resistant disease. Up to 25 administered doses of bevacizumab per patient have granted progression-free survival for these patients. Bevacizumab among this group of patients was tolerated with acceptable toxicity.

Bevacizumab was also used as a maintenance therapy following the treatment with standard chemotherapy. In the phase III studies (10, 11) progression-free survival increased by 1.7–2.9 months when given bevacizumab as a combination therapy followed by bevacizumab as maintenance therapy compared to standard chemotherapy. In our study, 15 patients received bevacizumab as a maintenance therapy with six patients still receiving the treatment at analysis.

5 CONCLUSION

Although the number of patients in this retrospective survey is rather limited and hence, no firm conclusions can be drawn, this paper describes real-life experience with bevacizumab outside controlled trial settings.

Bevacizumab treatment was overall well tolerated especially in first-line. Most severe adverse events occurred in heavily pretreated patients. Mild hypertension was a common adverse event, and interestingly, it was associated with a longer PFS in patients with recurrent OC. One gastrointestinal perforation occurred in our population, which is consistent with previous studies. The incidence of proteinuria was likewise in line with previous studies. No venous or arterial thromboembolic events were reported.

The response rates in patients with recurrent OC were consistent with previous studies. Patients with a platinum-resistant disease responded with a higher rate than what has been reported previously. There were differences in survival in the first-line treatment group compared to the randomized controlled GOG 218 and ICON7 trials. Differences between study populations regarding disease stage and debulking status can explain the differences. Promising results were noted in cervical cancer patients. A partial response lasting 16 months was observed in this group.

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